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role and its coordination with the core DNA-binding domain is highly debated. Here I present how we use single-molecule techniques to characterize the search process and disentangle the roles played by these two DNA-binding domains in the search process. We demonstrate that the C-terminal domain is capable of rapid translocation, while the core domain is unable to slide and instead hops along DNA. These findings are integrated into a model, in which the C-terminal domain mediates fast sliding of p53, while the core domain samples DNA by frequent dissociation and re-association, allowing for rapid scanning of long DNA regions. The model further proposes how modifications of the C-terminal domain can activate ''latent'' p53 and reconciles seemingly contradictory data on the action of different domains and their coordination.

7-Subg
Solution NMR as an Investigational Tool for Disordered and Partly Folded Proteins
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The chaperone Hsp90 interacts with a relatively large set of proteins, termed client proteins, but their state, whether folded, partly folded or alternatively folded is not clear. NMR experiments on client proteins in the presence and absence of Hsp90 provide unprecedented insights into the conformational states of client proteins. As well, the NMR spectra of the chaperone itself in the presence of the client protein and of co-chaperones give information on interaction sites. NMR experiments on such large proteins and protein complexes are difficult both of execution and interpretation, but allow the formulation of hypotheses that can be tested by other spectroscopic means. We find that several client proteins form molten globule-like states when in the presence of Hsp90. The interactions between one client protein, the p53 DNA-binding domain, and fragments of Hsp90 of various sizes, comprising 1 and 2 domains of the protein, up to the full-length dimeric protein showed loss of signal intensity of the p53 resonances in the complex, from which we infer the prtesence of a state with secondary structure indistinguishable from that of the free protein, but containing a manifold of states that are in intermediate exchange on the NMR time scale. Further evidence for the loose and flexible nature of the bound p53 client is provided by the fluorescence behavior of the dye 1-anilinonaphthalene-8-sulfonic acid (ANS) and by comparison of H/D exchange rates of the amide protons of the p53 DNA binding domain. Hsp90 itself appears to make highly dynamic interactions with the client protein, which are modified in the presence of co-chaperones such as p23. We conclude that the interaction between Hsp90 and p53 is complex, and involves a structural change in the client protein to a loosened state.

8-Subg
Role of Disorder in T-Cell Signaling
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The T cell receptor plays a central role in the initiation of adaptive immune responses by recognizing microbial peptides bound to MHC molecules. Signaling through the receptor occurs through three associated signaling dimers (the CD3 dimers). We have shown that the cytoplasmic domain of the CD3 epsilon chain is membrane bound in live cells. Furthermore, we determined the NMR structure of the CD3 epsilon cytoplasmic domain in its lipid-bound state. The structure showed that the two critical tyrosines are inserted into the hydrophobic part of the lipid bilayer. We therefore propose that membrane binding prevents premature receptor activation.

9-Subg
Sorting with Disorder at Nuclear Pores
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Macromolecular traffic between the nucleus and cytoplasm of cells is mediated by karyopherins and is gated at nuclear pores (NPCs) by intrinsically-disordered proteins featuring phenylalanine-glycine repeats: the FG nucleoporins. Despite their dynamic nature, these FG nups adopt distinct categories of disordered structure with unique functions. Some are collapsed-coil globules that stick to each via FG repeats, and others are highly-extended coils that repel each other. Remarkably, these structures are segregated within FG nups and at NPCs to create a quaternary gating structure that appears suspended in the middle of the nuclear pore termed the transporter or plug. We describe how this 'ghostly' structure, whose existence has been debated for decades, is naturally-formed by more than one hundred intrinsically-disordered proteins acting collectively. We will also discuss how the distinct categories of disordered nup structures serve different functions in karyopherin-mediated transport.

10-Subg
Role of Disorder in Clathrin Lattice Assembly
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Assembly of clathrin lattices is mediated by assembly/adaptor proteins which contain domains that bind lipids or membrane bound cargo proteins, and clathrin binding domains (CBDs) that recruit clathrin. Here we characterize the interaction between clathrin and a large fragment of the CBD of the clathrin assembly protein AP180. Mutational, NMR chemical shift, and analytical ultracentrifugation analyses allowed us to precisely define two clathrin binding sites within this fragment, each of which is found to bind weakly to the N-terminal domain of the clathrin heavy chain (TD). The locations of the two clathrin binding sites are consistent with predictions from sequence alignments of previously identified clathrin binding elements and, by extension, indicate that the complete AP180 CBD contains ~12 degenerate repeats, each containing a single clathrin binding site. Sequence and circular dichroism analyses have indicated that the AP180 CBD is predominantly unstructured and our NMR analyses confirm that this is largely the case for the AP180 fragment characterized here. Unexpectedly, unlike the many proteins which undergo binding coupled folding upon interaction with their binding partners, the AP180 fragment is similarly unstructured in its bound and free states. Instead, we find that this fragment exhibits localized beta turn-like structures at the two clathrin binding sites both when free and bound to clathrin. These observations are incorporated into a model in which weak binding by multiple, pre-structured clathrin binding elements regularly dispersed throughout a largely unstructured CBD allows efficient recruitment of clathrin to endocytic sites and dynamic assembly of the clathrin lattice.

Subgroup: Bioenergetics

11-Subg
Mitochondria and Sporadic Neurodegenerative Disease
Russell H. Swerdlow.
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Late-onset neurodegenerative diseases can affect cognitive, movement, motor, or coordination functions. Particular neurodegenerative disease phenotypes can be etiologically heterogeneous, such that a particular ''disease'' may have different origins. Despite this, it is assumed that from a mechanistic perspective phenotypically similar diseases may at least share final common pathways. One pathologic feature observed in a number of neurodegenerative disorders is mitochondrial dysfunction. In Mendelian versions of particular neurodegenerative diseases, the presence of an abnormal gene product may interfere with mitochondrial function and through this induce neurodegeneration. In sporadic versions of these diseases, in addition to mediating dysfunction, evidence further suggests mitochondria may play an upstream role and potentially even initiate dysfunction. Because mitochondria are also implicated in aging, mitochondrial etiologies may prove particularly relevant to diseases whose incidence and prevalence progressively increase with advancing age. This conceptual approach has been used to classify a series of ''neurodegenerative mitochondriopathies'', define a sporadic Alzheimer's disease mitochondrial cascade hypothesis, and guide therapeutic development strategies.

12-Subg
Modulating the Mitochondrial F0F1-ATPase as Therapeutic Strategy for Systematic Autoimmunity
Gary D. Glick.
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This lecture will discuss how modulation of the mitochondrial ATPase can provide a selective, non-immunosuppressive mechanism for the treatment of